Remarks/Arguments

1. Amendments

The brief description of the drawings in the specification has been amended to reflect the numbered subparts, as requested by the Examiner. The amendment does not introduce new matter into the specification.

2. Objection to the Amendment to the Specification at page 5, line 3.

In the Final Office Action dated 5/10/07, the objection to the amendment to page 5, line 3, paragraph [0027] filed 6/12/06 under 35 U.S.C. 132(a) was maintained because it allegedly introduces new matter into the disclosure.

Applicants amended the paragraph as follows:

> The full-length polypeptide of the present invention as set forth in SEQ ID NO:2 has a putative signal sequence which comprises amino acid 1 through amino acid 45 of SEQ ID NO:2 which aids in secretion of the polypeptide from the cell. The polypeptide is further processed wherein amino acid 46 through amino acid ~~214~~ 259 of SEQ ID NO: 2 are cleaved from the polypeptide since this stretch of amino acids is a putative precursor sequence. Further, amino acid ~~264~~ 310 through amino acid 344 represent a putative transmembrane portion which is thought to be necessary to direct the polypeptide to particular target locations for the carrying out of biological functions as herein after described. The transmembrane portion may also be cleaved from the polypeptide such that the putative soluble portion of the polypeptide of the present invention comprises amino acid ~~215~~ 260 through amino acid ~~264~~ 309 of SEQ ID NO:2.

In arguments filed 2/23/07, applicants explained that the specification was amended at page 5, line 3, paragraph [0027] to correct obvious typographical errors regarding the numbering of the functional regions within the amino acid sequence of SEQ ID NO:2 as mentioned on page 5 of the specification. However, the rejection was maintained based on the requirements of MPEP 2163.07 and *In re Oda*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971). Applicants respectfully request reconsideration of the Examiner's position, and maintain that their proposed amendment does not introduce any proscribed new matter, and is completely consistent with requirements outlined in MPEP 2163.07 and *In re Oda*.

First, it is clear that new matter does not encompass material that is *inherently* disclosed in the original application cannot constitute new matter. See, e.g., *Koito Mfg. Co., Ltd. v. Turn-Key Tech., LLC*, 381 F.3d 1142 (Fed. Cir. 2004). In *Koito*, the applicant amended the

specification through a certification of correction to alter the definition of the thickness of the claimed "flow channel" element in the description of the first and second embodiments of the application; the correction effectively redefined the flow channel thickness. Appellants argued that the correction improperly introduced new matter unsupported by the original specification, which disclosed a different flow channel thickness, and broadened the scope of the claims. The Court disagreed, noting that the original (uncorrected) description would have excluded the preferred embodiment shown in Figures 4 and 5 of the patent, which disclosed a flow channel having thicknesses conforming to the amendment. "Because the amended material is inherently contained in the original application, it cannot constitute new matter." 381 F.3d at 1154. The reasoning of *Koito* is equally applicable to the present facts, because the proposed correction addresses matter that is *already* inherently present in the original application. Specifically, applicants seek to amend the endpoints for the soluble portion to match the ranges already disclosed in Example 2 of the original application, which states that the soluble portion runs from nucleotides 1100 through 1248 of SEQ ID NO:1, which corresponds to residues 260 and 309 respectively.

Further, applicants respectfully disagree with the Examiner's conclusion that the proposed changes violate the requirement outlined in *In re Oda* that "the invention described in the original patent must not be changed." As the case law makes clear, when the *inherent* nature of the claimed invention is disclosed in the original application, and the correction merely seeks to clarify the scope or nature of the claimed invention, the correction is proper. As the case law confirms, changes to the structural description (including numbering and location of sub-fragments of a claimed protein) are typographical in nature and therefore do not violate the new matter prohibition of 35 U.S.C. § 132. See, e.g., *Ex Parte Marsili*, 214 USPQ 904 (Pt. & Trademark Bd. Appeals 1979). For example, in *Marsili*, the Board of Appeals overturned the final rejection of a generic product claim, disagreeing with the examiner's finding that the claim contained proscribed new matter. During prosecution, applicant had sought to amend the specification as well as the claim at issue to alter the structure of the claimed compound. As the Court explained, applicants had initially considered their compounds they prepared contained an imidazoline ring, but later discovered that the claimed ring structure was in fact the more stable imidazole structure. The proposed amendment revised the specification and rejected claim to

recite the imidazole instead of the imidazoline. The Court found that the amendment did not introduce new matter, based on the reasoning that the revised structure was an *inherent* characteristic of the claimed compounds. Based on evidence that structural formula originally assigned to the claimed compounds had to be incorrect, the Court held that "the products described, exemplified and claimed by Appellants inherently had and have now the structure given by the amendment" and that the proposed changes did not constitute new matter. 214 USPQ at 906. The Court also noted that "[t]o refuse correction of the structural formula of Appellants' claimed compounds, . . . would lead to the absurdity of a patent which teaches the public in its specification the wrong scientific formula for new products." *Id.*

The reasoning underlying the *Marsili* decision has since been repeatedly applied to reject arguments of new matter based on structural corrections to claimed compounds, including situations involving claims drawn to DNA sequences. See, e.g., *Ex Parte D*, 27 USPQ2d 1067 (Bd. Pat. App. & Interf. 1993) (relying on *Marsili* and associated decisions to find that a prior art reference under 102(e) did not violate the new matter prohibition merely because the sequence of the claimed DNA was amended during prosecution) ("[A] gene is a chemical compound, albeit a complex one. . . . Thus, it is manifest that the prior decisions involving chemical compounds are equally applicable to claims directed to the present subject matter."). Under *Marsili* and its progeny, applicants' amendment is likewise proper because it seeks only to correct typographical errors associated with the numbering of the endpoints of the soluble portion and the associating flanking regions and does not change the inherent nature of the claimed invention, which remains the very same protein disclosed and claimed in the original application.

Applicants also respectfully disagree with the Examiner's conclusion that the proposed correction violates the requirements set forth in MPEP 2163.07 that "[a]n amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction." Applicants respectfully submit that both requirements are satisfied. The first requirement, recognition of the error, is clearly satisfied because the error is evident from the *original disclosure* of the specification, which was internally inconsistent regarding the location of the soluble portion of the claimed protein. Specifically, page 5 of the original specification states that "the putative soluble portion of the polypeptide of the present invention comprises amino

acid 215 through amino acid 264 of SEQ ID NO:2." *See* Specification filed 8/21/03 at page 5, line 3, paragraph [0027]. However, this statement is contradicted by other, more exact, portions of the specification, including working example 2 that describes a procedure for "Cloning and Expression of TGFα-HII using the Baculovirus Expression System." *See* Specification filed 8/21/03 at pages 29-31. Example 2 instructs the skilled artisan to prepare a fusion protein comprising the putative soluble portion by cloning the soluble portion using oligonucleotide primers, named SEQ ID NO:9 and SEQ ID NO:10, directed to each end of the region spanning nucleotides 1100 through 1248 of SEQ ID NO:2. Specification filed 8/21/03 at page 29, paragraph [0146]. On referring to nucleotide sequence SEQ ID NO:1 and its aligned amino sequence SEQ ID NO:2, it is apparent that the DNA sequence of these primers are found at nucleotides 1100 and 1248 as specified on page 3 of the sequence listing appended to the originally filed specification. However, the starting point of these oligonucleotide sequences do *not* correspond to amino acid residues 215 and 264 as specified on page 5. Instead, they correspond to residues 260 and 309 respectively.

According to the Examiner, "the skilled practitioner would have no way of recognizing the error from the specification and claims alone." Applicants respectfully submit that the skilled artisan would readily recognize the clear error from the specification itself, because the disclosure of paragraph [0027] of the is contradicted by the clear disclosure of Example 2 regarding the position of the nucleotide (and hence by extension the amino acid residue) where the soluble portion begins. Accordingly, applicants respectfully disagree with the examiner's conclusion that the error could only be recognized "by using information outside of the specification, information that is new matter." As the record makes clear, the error is clear from the original content of the specification as filed.

The second requirement of MPEP 2163.07, recognition of the appropriate correction, is also satisfied here. Further, it is apparent from the record that the person of ordinary skill in the art would also recognize the appropriate correction to the error without recourse to new matter. As described above, Example 2 provides the sequence of the oligomers named SEQ ID NO:9 and SEQ ID NO:10, which are directed to each end of the putative soluble portion of SEQ ID NO:2. Based on the sequence of these primers, it is readily apparent to the skilled artisan that SEQ ID NO:9 anneals to a region beginning with amino acid residue 260 and that SEQ ID NO:10 anneals

to a region ending with amino acid residue 309. Based on the specific and detailed sequence information provided in Example 2, the skilled artisan would recognize that the mistake must lie in the conflicting statement on page 5 of the specification, which merely identifies the endpoint residues in passing and does not provide any supporting detail. Furthermore, it is clear from the entire disclosure of the specification that the error must lie within paragraph 0027 rather than Example 2, because the remainder of the specification accords with this interpretation, and contradicts the statement in paragraph [0027]. The skilled reader would accordingly recognize that the appropriate correction is to replace the reference to these residues with references to residue 260 and 309 respectively.

From this correction, it would be equally obvious that the residues defining the C-terminal endpoint of the putative cleaved region, which precedes the soluble portion, should correspondingly and appropriately be corrected from position 214 to position 259 (otherwise the preceding correction, necessitated by the obvious error in the specification, would be rendered meaningless).

Applicants respectfully disagree with the Examiner's position that the selective addition of +45 to certain (but not all) amino acid regions on page 5 "require one to arbitrarily decide which parts of the disclosure are in error and which are correct." Final Office Action at page 5. It appears that the Examiner misunderstands the fundamental nature of the error sought to be corrected. Applicants do *not* seek to indiscriminately increase the numbering of all residues of SEQ ID NO:1 by +45, since that is *not* the nature of the typographical error appearing in paragraph [0027]. Rather, the error specifically concerns the proper location for the endpoints of the soluble portion. Such error, by its very nature, also necessitates a corresponding revision to the numbering of residues immediately flanking these endpoints. Once the skilled reader recognized the obvious error and the corresponding correction, it would be equally obvious that the corresponding residues *immediately flanking* the soluble portion should correspondingly be modified so as to match the new endpoints of the soluble portion. However, since no other internal inconsistencies are apparent, the skilled reader would not be inclined to alter any other residues of the originally disclosed sequence, and would not conclude that similar changes to the endpoints for domains *not immediately flanking* the soluble portion are also required. As a

logical (as opposed to arbitrary) conclusion, all other residues would remain unaltered, since they are not implicated by any inconsistencies appearing in the specification.

3. Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 25 and 31-44 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[1] [2];. The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[3] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. [4] [5]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[6] , the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).[7] Further, The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[8]

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[1] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983)
[2] *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991)
[3] *See, e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.
[4] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000)
[5] *See also* MPEP §2163 II(A).
[6] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984)
[7] *See also* MPEP §2141.03.
[8] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added)

The Disclosure Provides Sufficient Written Description for the Claimed Invention

Claim 25 recites a method for the treatment of a patient having need to inhibit TGFα-HII comprising: administering to the patient a therapeutically effective amount of an antibody that inhibits TGFα-HII and is capable of binding to a TGFα-HII polypeptide or fragment.

When the instant specification is read as a whole, it is clear that the inventors were in possession of the claimed method for treatment with antibodies capable of binding to a TGFα-HII polypeptide or fragment.

The Examiner states that no basis is seen for administering chimeric antibodies (claim 41) humanized antibodies (claim 42) single chain antibodies (claim 43) and FAB fragments (claim 44) in the specification.

Support for claims 41-44 can be found for example at page 26. More specifically support for chimeric antibodies can be found for example at page 26, para [0127], support for human antibodies can be found for example at page 26, para [0127], and page 26, para [0128] (administering to "preferably a nonhuman "animal is an implicit disclosure of administering also to humans); support for single chain antibodies can be found for example at page 26, para [0127]; and support for FAB fragments can be found, for example, at page 26, para [0127]. Withdrawal of this rejection is respectfully requested

The Examiner states that although original claim 19 does list ranges 1-374 and 46-374 as well as a polypeptide encoded by the cDNA contained in the ATCC deposit, no basis is seen for the other named ranges.

Applicant has indicated that the ranges in claim 25 were amended to reflect the correction in amino acid ranges as discussed for page 5 of the specification. Support for these corrections is provided in the specification for the reasons set forth above. Withdrawal of this rejection is respectfully requested

The Examiner states that a discussion as to what amino acids are identified as the leader sequence or transmembrane sequence cannot be construed as providing a basis for claiming antibodies that specifically bind to particular fragments.

In response the Examiner is directed to original claim 21 which claimed an antibody against the polypeptide of claim 19. As discussed above claim 19 provided the listed ranges as well as different sized fragments of the polypeptide. Clearly there was written support in the

application for an antibody against the polypeptides set forth in original claim 19. Withdrawal of this rejection is respectfully requested

The Examiner indicates that the information concerning the deposit on page 6 of the specification does not make clear what cDNA sequence is actually contained in the ATCC deposit.

Applicant respectfully requests that the Examiner clarify this objection because the Applicant does not understand the Examiner's concern. Applicant did state in the prosecution of parent application 09/227,853 that DNA encoding the full-length sequence of SEQ ID NO:2 is present in the recited deposit.

The Examiner notes that the specification has been amended to change the date of deposit of ATCC 97160 from 15 May 1995 to 24 May 1995. The Examiner requests that Applicant supply copies of the same evidence presented in Parent application 09/227,853 to complete the instant specification.

In response Applicant encloses a copy of the ATCC Receipt which sets forth the date of May 24, 1995 for receipt of deposit 97160. Withdrawal of this rejection is respectfully requested.

4. Rejection under 35 U.S.C. 112, first paragraph, enablement

Claims 25 and 31-44 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The specification allegedly fails to identify those patients having need to inhibit TGFα-HII. It is allegedly not known what characteristics or medical conditions such patients must possess. Further the specification allegedly fails to identify any antibodies that bind to any portion of SEQ ID NO:2 that are capable of inhibiting TGFα-HII either in vitro or in vivo. Finally the Examiner states that the specification allegedly fails to identify any fragments of SEQ ID NO:2 (including any 30 to 50 contiguous amino acid ranges) or any polypeptides at least 70% identical to SEQ ID NO:2 that could be used to generate antibodies that have the property of in vivo inhibition of TGFα-HII for any therapeutic purpose. For the following reasons Applicants disagree with this analysis.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation.[9] [10] Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[11] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue.[12] [13]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). The most important factors that must be considered in this case include: 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification; 4) the state of the prior art; and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important"[14] [15]. "Limitations and examples in the specification do not generally limit what is covered by the claims" MPEP § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[16]

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[9] MPEP §2164.0120

[10] *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998))
United States v. Telectronics, Inc. 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998))

[11] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)

[12] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977)

[13] MPEP §2164.06.

[14] MPEP §2164.08

[15] *In re Marzocchi*, 439 F. 2d 220, 223-4, 169 USPQ 367, 370 (CCPA 1971)

[16] *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

The Disclosure provides sufficient information to enable the claimed invention

Claims 25 and 31-44 are directed to a method for the treatment of a patient having need to inhibit TGFα-HII comprising administering to the patient a therapeutically effective amount of an antibody that inhibits TGFα-HII and is capable of binding to a TGFα-HII polypeptide.

Applicants have amended claim 25 to cancel the recitation of a polypeptide which is 70% identical to the TGFα-HII.

The Examiner states that it is not known what characteristics or medical conditions such patients must possess.

The specification clearly indicates that antibodies capable of binding to an TGFα-HII polypeptide would be useful for the treatment of a number of medical conditions. Page 18, paragraph [0093] states that potential antagonist compounds include an antibody ...which binds to the polypeptide. Page 19, paragraph [0096] states that antagonists may be employed to treat neoplasia, for example cancers and tumors. Page 19, paragraph [0097] states that antagonists to the polypeptides of the present invention may also be used therapeutically for the treatment of certain skin disorders, for example psoriasis. Page 24, paragraph [0119] states that antibodies specific to TGFα-HII may be used for cancer diagnosis and therapy, since many types of cancer cells up-regulate various members of the TGFα family during the process of neoplasia or hyperplasia. Withdrawal of this rejection is respectfully requested.

The Examiner states that the specification allegedly fails to identify any antibodies that bind to any portion of SEQ ID NO:2 that are capable of inhibiting TGFα-HII either in vivo or in vitro.

As discussed above, the specification provides, for example, on page 26, paragraphs [0127] – [0130] methods for the generation of antibodies capable of inhibiting TGFα-HII. The specification provides the complete amino acid sequence for TGFα-HII and the Examples provides methods of expressing and isolating the protein in E. coli (Example 1), baculovirous (Example 2) and COS cells (Example 3). One skilled in the art given the disclosure in the specification and the knowledge in the art could readily generate antibodies capable of inhibiting TGFα-HII. Withdrawal of this rejection is respectfully requested.

Finally the Examiner states that the specification allegedly fails to identify any fragment of SEQ ID NO:2 (including any 30 to 50 contiguous amino acid ranges) or any polypeptides at

least 70% identical to SEQ ID NO:2 that could be used to generate antibodies that have the property of in vivo inhibition of TGFα-HII for any therapeutic purpose.

Applicants have amended claim 25 to cancel the recitation of least 70% identical to SEQ ID NO:2 rendering this part of the rejection moot. As discussed above the specification does provide support for any fragment of SEQ ID NO:2 (including any 30 to 50 contiguous amino acid ranges) that could be used to generate TGFα-HII antibodies. Page 26, paragraphs [0127]-[130] provide methods for generation of antibodies capable of inhibiting TGFα-HII from fragments. Withdrawal of this rejection is respectfully requested.

The Examiner states that the specification fails to provide that there is a correlation between any in vitro antibody binding and any in vivo inhibition of TGFα-HII for any therapeutic purpose. Applicants have amended claim 25 to recite that the antibody inhibits TGFα-HII. Accordingly Applicants are claiming antibodies which will function to inhibit TGFα-HII. As discussed above the specification provides support for the generation of such antibodies at page 26, paragraphs [0127] – [0130]. One skilled in the art given the specification could generate antibodies which inhibit TGFα-HII. Withdrawal of this rejection is respectfully requested.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Please charge any additional fees, including additional fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39766-0151US D2).

Respectfully submitted,

(Pangan Gao 43,626)
on behalf of
Ginger Dreger

Date: March 10, 2008

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)
Human Genome Sciences, Inc.
Attention: Robert H. Benson
9410 Key West Avenue
Rockville, MD 20850

RECEIVED
JUN 23 1995
HGS LEGAL DEPT.

Deposited on Behalf of: Human Genome Science, Inc.

Identification Reference by Depositor:	ATCC Designation
DNA Plasmid, 503459 (HGS Docket PF174PCT.US)	97160
DNA Plasmid, 655101 (HGS Docket PF101P1)	97161
DNA Plasmid, 79365 (HGS Docket PF194)	97162
DNA Plasmid, 668850 (HGS Docket PF198)	97163

The deposits were accompanied by: _ a scientific description _ a proposed taxonomic description indicated above.

The deposits were received May 24, 1995 by this International Depository Authority and have been accepted.

AT YOUR REQUEST:

X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years after the date of deposit, and for a period of at least five years after the most recent request for a sample. The United States and many other countries are signatory to the Budapest Treaty.

The viability of cultures ATCC 97160, 97162 and 97163 were tested June 6, 1995 and ATCC 97161 was tested June 8, 1995. On those dates, the cultures were viable.

International Depository Authority: American Type Culture Collection, Rockville, Md. 20852 USA

Signature of person having authority to represent ATCC:

Annette L. Bade, Director, Patent Depository

Date: June 14, 1995

cc: Greg D. Ferraro, J.D.